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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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NEKTAR THERAPEUTICS  
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EXAMINER

MONDESI, ROBERT B

ART UNIT PAPER NUMBER

1653

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/789,956	Applicant(s) BOSSARD ET AL.	
	Examiner Robert B. Mondesi	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 16 December 2005.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-62 is/are pending in the application.
- 4a) Of the above claim(s) 31-61 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-30 and 62 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 July 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 16, 2005 has been entered.

### ***Status of the claims***

**Claims 1-62** are pending. **Claims 31-61** are withdrawn for pertaining to non-elected subject matter. **Claims 1-30 and 62** are presently under examination.

### ***Information Disclosure Statement***

The IDS filed March 28, 2005 has been received and is signed and considered, a copy of the PTO 1449 is attached to the following document.

### ***Withdrawal of Objections and Rejections***

The objections and rejections not explicitly restated below are withdrawn.

### ***Maintenance of rejections***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections - 35 USC § 103***

**Claims 1, 3-4 and 8-11** remain rejected under 35 U.S.C. 103(a) as being unpatentable over Minamino et al. in view of Greenwald.

**Claims 1, 14 and 16** remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rostin et al. in view of Greenwald.

The above rejections were explained in the Office action mailed December 23, 2004.

***Response to applicant's arguments***

In regards to the rejection of **claims 1, 3-4 and 8-11** under 35 U.S.C. 103(a) as being unpatentable over Minamino et al. and Greenwald, the applicants assert that Minamino et al. teach "structurally useful" modified Factor VIII conjugate comprising about 70-110 polyalkylene glycol polymers and in contrast the applicants claim a conjugate of one, two or three water-soluble polymers covalently attached to Factor VIII moiety and furthermore, Greenwald does not remedy the deficiencies of Minamino et al. with regards to the claimed invention.

Applicants' arguments have not been found persuasive. The rejected claims depend from an independent base claim that uses the transitional phrase comprising with regards to the number of water-soluble polymers covalently attached to Factor VIII Moiety; therefore there is no upper limit to the number of water-soluble polymers attached to the Factor VIII moiety. On Page 22, section 0100, in the specification of the present application it is clearly stated that, " a conjugate of the invention comprises a water-soluble polymer covalently attached to a Factor VIII moiety. Typically, for any

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given conjugate there will be one to three water-soluble polymers covalently attached to one or more moieties having Factor VIII activity. In some instances, however, the conjugate may have 1, 2, 3, 4, 5, 6, 7, 8, or more water soluble polymers individually attached to a Factor VIII moiety". In view of applicants' disclosure in the specification of the present application, it is apparent that the applicants have not contemplated an upper limit to the number of water-soluble polymers attached to the "conjugate" of the invention and in conjunction with the fact that the applicants have used the transitional phrase "comprising", the conjugate claimed in claim 1 can not be considered as a conjugate having only 1-3 attached water-soluble polymers; therefore the conjugate of Minamino et al., even though having 70-110 attached water-soluble polymers, meets this particular limitation of the claim 1. Examiner would also like to point out that we regards to the limitations of **claims 3-4 and 8-11**; Greenwald clearly has disclosed water-soluble polymers such as polyethylene glycol with a nominal average molecular weight in the range of from 53,000 to 75,0000 and the motivation to combine the two references. Greenwald discloses biologically active molecules, including Factor VIII (Column 7, lines 33-37) covalently bound to poly(ethylene oxides), such as polyethylene glycol, with nominal molecular weight in the range of from 53,000 to 75,0000 (column 3, lines 51-54).

In regards to the rejection of the **claims 1, 14 and 16** under 35 U.S.C. 103(a) as being unpatentable over Rostin et al., 2000 in view of Greenwald, the applicants assert that, Rostin et al. describe the preparation of several compositions of conjugates, each of Rostin et al.'s described compositions of conjugates is prepared using polymers

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having molecular weights of 3,000 Daltons or 5,000 Daltons. Thus, Rostin et al., neither discloses nor suggests conjugates comprising one, two or three water soluble polymers attached to a Factor VIII moiety, wherein each water soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000. The applicants also assert that Greenwald does not cure the deficiencies of Rostin et al.

Applicants' arguments have not been found persuasive. As indicated above the conjugate of the invention is not limited to a particular number of water-soluble polymers attached to the Factor VIII moiety. In light of the broadest reasonable interpretation of the claims in view of the specification and particularly with regards to independent claim 1, the conjugate of the invention can be a Factor VIII moiety covalently attached to at least 1 water-soluble polymer and there being no upper limit for the number of covalently attached polymers. Rostin et al., certainly disclose a number of Factor VIII moieties that have at least one water-soluble polymer attached and in particular Rostin et al. disclose B-Domain deleted Factor VIII moieties. It is true that Rostin et al do not disclose a Factor VIII moiety conjugated to a water-soluble polymer, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 but that that is precisely why the rejection of the claims is under 35 U.S.C. 103(a) as being unpatentable over Rostin et al. in view of Greenwald. With all due respect to the applicants' assertions, Greenwald clearly has disclosed water-soluble polymers in the range of 6,000 to 150,000 and the motivation to combine the two references. Greenwald discloses biologically active molecules, including Factor VIII (Column 7, lines 33-37) covalently bound to poly(ethylene oxides), such as

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polyethylene glycol, with nominal molecular weight in the range of from 6,000 to 150,000 (column 3, lines 51-54). It would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently bind Factor VIII to poly(ethylene oxides), such as polyethylene glycol, with nominal molecular in the range of from 6,000 to 150,000 Daltons for the advantages reduced immunogenecity and increased bio-availability as taught by Rostin et al. and Greenwald, see Rostin et al. at page 1, columns 1-2, and Greenwald at column 1, lines 17-29.

***New Objection(s) and Rejection(s)***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 26-30** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

**Claims 26-30** recite the limitations "an amide linkage", "a secondary amine linkage", "a carbamate linkage", "a thioether linkage", "a disulfide linkage" in line 2 of each claim respectively. There is insufficient antecedent basis for these limitations in the claims. **Claim 1** does not state the presence of a linkage, in particular with regards to a linkage between the water-soluble polymer and the Factor VIII moiety; but rather it states that the water-soluble polymer is covalently attached to the Factor VIII moiety. It is no clear from the language of the claim whether the mentioned linkage is between the

Factor VIII moiety and the water-soluble polymer or whether the linkage occurs anywhere in the structure of the conjugate.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62** are rejected under 35 U.S.C. 103(a) as being unpatentable over Minamino et al. United states Patent 6,037,452 (cited in the IDS filed October 28, 2004) in view of in view of Davis et al. United States Patent 4,179,337 (cited in the IDS filed November 15, 2004).

Minamino et al. disclose Factor VIII, Factor IX, Factor VIIIa, Factor IXa and analogous polypeptides covalently bonded through a bonded group to poly(alkylene oxide) (column 2, lines 61-64).

Minamino et al. disclose further that the invention is not only applicable to factor VIII and factor IX obtained from blood but also to Factor VIII and Factor IX manufactured by recombinant DNA procedures (column 3, lines 15-18).

Minamino et al. teach that the present invention is not limited to normal Factor VIII (i.e., bound to Factor VIII:vWF) and Factor IX, but also to Factor VIII:C and various active species of any of them, or inactive precursor species (whether of longer or shorter chain length than purified Factor VIII or Factor IX as obtained from blood fractionation) and the Factor VIII and Factor IX, as well as the various activated forms and analogous structures thereof (various analogous structures with deletion, substitution, addition, etc. of one or more amino acids, but retaining the Factor VIII and/or Factor IX biological activity can be prepared, especially through recombinant DNA procedures) as useful herein, should contain an amino terminus and a carboxyl terminus. In addition, linkage along the polypeptide chain or chains forming the same is generally of the amide type as is well known, with some modifications thereof through any intra or inter-chain bonding (Column 3, lines 28-43) and the modified Factor VIII prepared as described above can be purified according to conventional procedures, lyophilized and stored (Column 7, lines 30-32).

Minamino et al. also teach that bonding of the poly(alkylene oxide) thereto can occur not only at terminal portions of the polypeptide, but also along the chain(s) thereof to form side-chains of poly(alkylene oxide) and it is believed that the linking most likely involves formation of covalent bonds using intermediate linking or coupling

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reagents; however, other types of bond formation are contemplated herein such as ionic bonds, van der Waals force bond, and so forth. Furthermore, the poly(alkylene oxide) can be modified so that only one terminus thereof can participate in the reaction with the peptide (whether or not through a coupling reagent) by preliminarily reacting the poly(alkylene oxide) with an alkyl group such as lower C<sub>1-5</sub> alkyl, especially methyl or ethyl, to form the corresponding alkoxy groups. Other OH protecting or activating groups can be employed, for example, acyl such as propionyl or other lower acyl (C<sub>1-5</sub>) groups as other protecting groups or, for example, phenyl or alkyl-substituted phenyl groups can be employed. The protecting groups used herein include those known in the art (Column 3, lines 44-61).

Minamino et al. teach further that most often, the poly(alkylene oxide) will react through a terminal hydroxyl group (the oxygen) or a modified terminal group such as, for example, when the terminal hydroxyl or hydrogen thereof has been replaced by another reactive moiety such as amino and the latter is especially useful where reaction is to be with carbonyl moieties of a linker or of the peptide itself and also known methods of forming an active derivative of the polyalkylene glycol can be employed herein such as the alkylation method, the acid azide method, the diazo method, the condensation method, etc., which are then allowed to react with free amino or carboxyl groups in the peptide to effect bonding (Column 2-3, lines 15-67 and lines 1-13).

Minamino et al. also disclose modified Factor VIII which has been conjugated to 2,4-bis (methoxypolyoxy-ethylene)-6-triazine wherein the polyoxyethylene moiety has a molecular weight of 5000 or more.

Minamino et al. do not disclose compositions comprising Factor VIII covalently bound to poly(ethylene oxides) such as polyethylene glycol with nominal molecular weight in the range of from 6,000 Daltons to 150,000 Daltons, 6000 Daltons to 100,000 Daltons or, 10,000 to 85,000 Daltons.

Davis et al. disclose biologically active molecules covalently bound to poly(ethylene oxides) such as polyethylene glycol that fall within the range of nominal molecular weight of 10,000 Daltons to 85,000 Daltons (column 2, lines 42-57).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently bind a Factor VIII moiety to poly(ethylene oxides), such as polyethylene glycol, that fall within the range of nominal molecular weight of 10,000 Daltons to 85,000 Daltons, for the advantages of reduced immunogenicity and increased bio-availability as taught by Minamino et al. and Davis et al., see Minamino et al. at column 1, lines 26-34 and Davis et al. at column 1, lines 15-50.

**Claims 1-10, 12-13, 21, 24-28 and 62** are rejected under 35 U.S.C. 103(a) as being unpatentable over Minamino et al. and Davis et al. as applied to **claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62** above, and further in view of Patton et al. United States Patent Publication No. 2003/0118510.

Minamino et al. and Davis et al. teach a conjugate comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety as mentioned above.

Minamino et al. and Davis et al. do not teach that the water-soluble polymer is a methoxy or hydroxy terminally end capped polyethylene glycol or that the water-soluble polymer is a linear or branched polymer.

Minamino et al. and Davis et al. also do not teach that the conjugate comprises, an amide linkage, an amine linkage or a carbamate linkage or that the composition comprising the conjugate is in liquid form and further comprises a pharmaceutically acceptable excipient.

Minamino et al. and Davis et al. do not teach that the composition is substantially free of non-covalently attached water-soluble polymers or is conjugated to polyethylene glycol that has a nominal average molecular weight in the range of from 20,000 Daltons to 85,000 Daltons.

Patton et al. teach that "PEG" or polyethylene glycol, as used herein, is meant to encompass any water-soluble poly(alkylene oxide). Most typically, PEGs for use in the present invention will contain the following structure, "

$\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2-$ , wherein the terminal groups or actual architecture of the overall PEG moiety may vary. One commonly employed PEG is end-capped PEG, wherein one terminus of the PEG is capped with a relatively inactive group, typically an alkoxy group such as methoxy ( $-\text{OCH}_3$ ), while the other terminus is a hydroxyl group that can then be subjected to chemical modification (Page 4, section 0056).

Patton et al. also teach that the water-soluble polymer may be linear or branched (Page 2, section 0014) and that the conjugate comprises, an amide linkage, an amine

linkage (Page 9, section 0102, lines 13-15) or a carbamate linkage (Page 9, section 0106).

Patton et al. teach further that the composition of the invention in is liquid form, further comprises a pharmaceutically acceptable excipient (Page 3, section 0028), is substantially free of non-covalently attached water-soluble polymers (Page 2, section 0021) and is conjugated to polyethylene glycol that has a nominal average molecular weight in the range of from 20,000 Daltons to 85,000 Daltons (Page 6, section 0086).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate Factor VIII to polyethylene glycol which has been end capped, wherein the polyethylene glycol is branched or linear and has a nominal average molecular weight within the range of from 20,000 Daltons to 85,000 Daltons, for the advantages of a formulation that is bioactive, physically and chemically stable, water soluble and has an extended-half life, as taught by Minamino et al., Davis et al. and Patton et al., see Patton et al. at page 2, section 0009, lines 15-16 and at page 6, section 0086, lines 1-7.

**Claims 1, 29 and 30** are rejected under 35 U.S.C. 103(a) as being unpatentable over Minamino et al. and Davis et al. as applied to **claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62** above, and further in view of Bentley et al. United States Patent Publication No. 2003/0161791.

The applied reference has a common inventor and a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a)

might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(I)(1) and § 706.02(I)(2).

Minamino et al. and Davis et al. teach a conjugate comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety as mentioned above.

Minamino et al. and Davis et al. also do not teach that the conjugate comprises a thioether, or a disulfide linkage.

Bentley et al. disclose a conjugate comprising a thioether (Page 9, section 0107, line 3 or a disulfide linkage (Page 10, section 0116, lines 27-28).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate polyethylene glycol to a biological molecule with a thioether, or a disulfide linkage for the advantages of a bioactive molecule that will retain a portion of the unmodified parent molecule's specific activity, as taught by Minamino et al., Davis et al. and Bentley et al., see Bentley et al. at page 9, section 0108, lines 1-25.

***Conclusion***


No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert B. Mondesi  
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Group 1653

  
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